Halogen bonding - the role and significance in interactions of ligands with class A GPCRs

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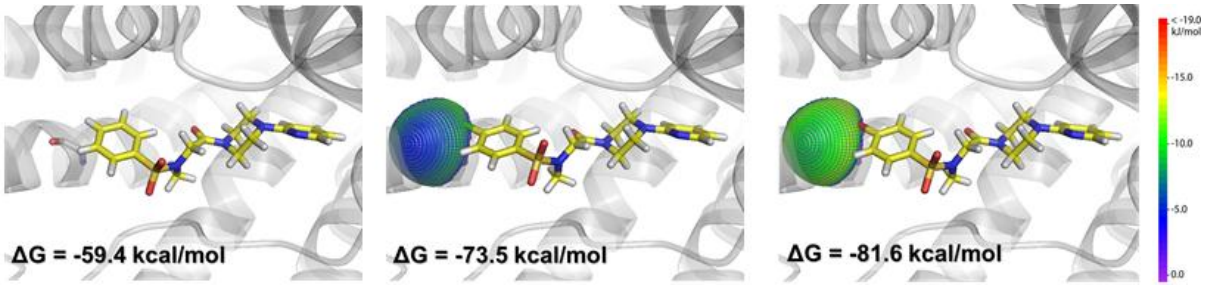
Halogen atoms are common features in biologically active compounds and drugs. Incorporation of halogen atoms into molecule structure changes its steric (volumetric), electrostatic and conformational properties, lipophilicity (influencing membrane permeability and the oral absorption), and may lead to even 300-fold increase in the affinity for a given biological target [1, 2]. Although, since many years, halogen atoms have been regularly used in drug optimization processes, only recently their role in protein–ligand complexes has been attributed to the formation of a specific, direct interactions called halogen bonds.
To date, systematic and comprehensive studies on the role and significance of halogen bonds in family A GPCRs have not been published. There are also no studies showing the use of the concept of halogen bonds in the rational design of potential ligands of these receptors.
Herein we report on a systematic molecular modeling approach, i.e. generation of X-SAR sets fetched from ChEMBL database, molecular docking, hybrid QM/MM calculations and plotting the interaction spheres [3], used to study the different role of halogen atoms in the interaction of ligands with all crystallized receptors of family A GPCRs (i.e. steric hindrances, interaction of positive σ-hole with negatively charged atoms of the protein). The performed calculations distinguished several hot-spot amino acids, as potential anchoring points for halogen bonding interaction.



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